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EXAMINER	
CAPPS, KEVIN J	
ART UNIT	PAPER NUMBER
1617	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/508,336	BIRCH ET AL.	
	Examiner	Art Unit	
	Kevin Capps	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,19,38,39,41 and 48-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,19,38,39,41 and 48-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 27, 3006, has been entered.

Status of the Claims

2. This Office Action is in response to the RCE filed on March 26, 2007. The Remarks and Amendments filed on December 27, 2006, have been entered and are considered herein. Claims 1-16, 19, 38, 39, 41, and 48-66 are pending and examined on the merits herein.

3. Claim 61 stands objected to because of an improper dependency. Applicant has not corrected the dependency, so the objection is maintained.

4. In view of Applicant's amendments specifying that the instantly claimed formulations maintain a buprenorphine plasma concentration of 0.4 to 5 ng/ml for at least 6 hours, the rejection of claims 48-52 under 35 U.S.C. 102(b) as being anticipated by Eriksen et al. (Applicant-cited reference on IDS: Eriksen, J. et al. *J. Pharm. Pharmacol.* **1989**, *41*, 803-805) is withdrawn. Specifically, the rejection is withdrawn

because, as Applicant points out on pp. 9-10 of the Remarks, the buprenorphine plasma concentration following administration of the formulation of Eriksen et al. falls to 0.23 ng/ml at 6 hours.

5. Claims 1-15, 38-39, and 41 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Eriksen et al. (Applicant-cited reference on IDS: Eriksen, J. et al. *J. Pharm. Pharmacol.* **1989**, *41*, 803-805), in view of Watts et al. (Applicant-cited reference on IDS: WO 98/47535), Reich et al. (Reich, I., et al. "Tonicity, Osmoticity, Osmolality and Osmolarity" Remington: The Science and Practice or Pharmacv, Nineteenth Edition, Volume 1. Easton, PA: Mack, **1995**. pp. 613-615), and Nairn (Nairn, J. G. Solutions, Emulsions, Suspensions and Extracts" Remington: The Science and Practice or Pharmacv, Nineteenth Edition, Volume 2. Easton, PA: Mack, **1995**. p. 1502). The rejection is maintained. Applicant's arguments are addressed below.

6. Claims 16 and 53-59 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Eriksen et al. (Applicant-cited reference on IDS: Eriksen, J. et al. *J. Pharm. Pharmacol.* **1989**, *41*, 803-805) in view of Koochaki (Applicant-cited reference on IDS: EP 0 571 671 A1). The rejection is maintained. Applicant's arguments are addressed below.

7. Claims 19 and 60-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eriksen et al. (Applicant-cited reference on IDS: Eriksen, J. et al. *J. Pharm. Pharmacol.* **1989**, *41*, 803-805.) in view of Williams et al. (Applicant-cited reference on IDS: WO 02/00195 A2, January 3, 2002). The rejection is maintained. Applicant's arguments are addressed below.

8. Claims 1-10, 12-16, 19, 56-59, and 63 stand provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 16, 19, 35, 36, 38-43, 45-47, and 49-56 of copending Application No. 10/508,315. This statutory type double patenting rejection is modified to address Applicant's amendments and the differences in claim scope.

9. Claims 11, 38, 39, 41, 48-55, 60-62, and 64-66 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-56 of copending Application No. 10/508,315. The rejection is maintained.

10. Claims 1, 13, 16, 19, 38-39, 41, 56-59, and 64-66 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2, 8, and 12 of U.S. Patent No. 6,387,917. The rejection is maintained. Applicant's arguments are addressed below.

Claim Objections

11. Claim 61 is objected to because of the following informalities: Claim 61 depends from claim 62. A claim should depend upon a preceding claim (MPEP § 608.01(n)). Appropriate correction is required.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claim 51 recites the limitation "A method according to claim 48". However, claim 48 is a composition claims. Therefore, there is insufficient antecedent basis for this limitation in the claim.

14. Claim 52 recites the limitation "A pharmaceutical composition according to claim 49". However, claim 49 is a method claim. Therefore, there is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 112

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims 48-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

17. There is no support in the specification for the new limitation in claims 48-52 that the therapeutic plasma concentration of buprenorphine is maintained for at least 6 hours. Applicant points to p. 18, l. 7, for support of the new T_{maint} limitations. However, at p. 18, ll. 5-10, there is no description of a nasal spray formulation comprising buprenorphine wherein the therapeutic plasma concentration of buprenorphine is

maintained for at least 6 hours after administration. Further, the figures showing the therapeutic plasma concentration of buprenorphine after nasal administration only show time points out to 6 hours. Thus, there is no support for this amendment in the instant specification.

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

20. Claims 1-15, 38-39, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eriksen et al. (Applicant-cited reference on IDS: Eriksen, J. et al. *J. Pharm. Pharmacol.* **1989**, *41*, 803-805.), in view of Watts et al. (Applicant-cited reference on IDS: WO 98/47535, October 29, 1998), Reich et al. (Reich, I., et al. "Tonicity, Osmoticity, Osmolality and Osmolarity" Remington: The Science and Practice or Pharmacy, Nineteenth Edition, Volume 1. Easton, PA: Mack, **1995**. pp. 613-615.),

and Nairn (Nairn, J. G. Solutions, Emulsions, Suspensions and Extracts" Remington: The Science and Practice or Pharmacy, Nineteenth Edition, Volume 2. Easton, PA: Mack, **1995**. p. 1502.).

21. Eriksen et al. teach an aqueous solution suitable for intranasal administration which comprises 2 mg/ml of buprenorphine as the salt buprenorphine hydrochloride. The composition of Eriksen et al. further comprises dextrose (see "The spray-device and the buprenorphine-spray solution" and "Procedure" on pp. 803-4). Due to the fact that Eriksen et al. do not add divalent metal cations into the composition during the preparation, it can be inferred that Eriksen et al. teach the composition as being substantially free of divalent metal cations.

22. Eriksen et al. also teach a method for the preparation of said composition ("The spray-device and the buprenorphine-spray solution" on p. 803).

23. Eriksen et al. teach a nasal delivery device loaded with said solution, wherein the nasal delivery device is a spray device ("The spray-device and the buprenorphine-spray solution" on p. 803).

24. Eriksen et al. do not teach that the solutions comprise pectin, wherein the pectin is at a concentration of 5-40 mg/ml, 10-30 mg/ml, or 10-40 mg/ml, and wherein the pectin has a degree of esterification of less than 50%, or a degree of esterification of from 10-35%. Eriksen et al. also do not teach the solution as having a pH of from 3-4.2 or from 3.5-4. Eriksen et al. do not teach the osmolality of the solution as being from 0.35 to 0.5 osmol/kg.

25. Watts et al. teach solutions that are substantially free of divalent metal ions and which comprise therapeutic agents and pectin with a low degree of esterification for administration intranasally, and specifically wherein the degree of esterification of pectin is less than 50%, and more preferably less than 35%. The pectin is present at a concentration of from 1 to 100 mg/ml (p. 2, lines 23-26; p. 9, lines 22-27; p. 11, line 21 - p. 12, line 5; p. 12, lines 22-27; Example 1; claims 1-2). Watts et al. also teach that said solution has a pH from "2 to 9, more preferably from 3 to 8 and most preferably from 4-7." (p. 16, line 29 -p. 17, line 3). Watts et al. teach that "the lower the DE of the pectin, the lower the pH at which the composition will gel. pH may be adjusted in accordance with techniques which will be well known to those skilled in the art" (p. 17, lines 3-6). Thus, Watts et al. suggest optimizing the pH of the composition within the disclosed preferred ranges using routine experimentation based on the pectin that is incorporated into the composition. Watts et al. also teach that the solutions comprising pectins and therapeutic agents should have a concentration of pectin greater than 4 mg/ml for solid gel formation upon intranasal administration (Example 1).

26. Nairn teaches that nasal solutions are usually isotonic (p. 1502).

27. Reich et al. teach, "The term isotonic, meaning equal tone, is in medical usage commonly used interchangeably with isoosmotic." (p. 613). Reich et al. also teach, "Serum osmolality often is stated loosely to be about 300 mOsmol/L." (p. 615).

28. Although the osmolality of the intranasal solution in the instant claim 11 is slightly higher than serum osmolality, this is necessitated by the amount of pectin that is required by the teachings of Watts et al. in order that the solution gels upon intranasal

administration (Example 1). Therefore, the osmolality of a solution for intranasal administration that comprises low DE pectin as the gelling agent should be close to isoosmotic and should have the required concentration of pectin to achieve gelling upon administration as taught by Narin, Reich et al., and Watts et al.

29. It would have been obvious to a person of ordinary skill in the art at the time of invention to incorporate pectins having a low degree of esterification into the solutions of Eriksen et al., to adjust the pH and osmolality of said solution to the appropriate ranges taught by Watts et al., to incorporate the solution into a spray device, and to intranasally deliver the solution in a method of inducing analgesia.

30. The person of ordinary skill in the art would have been motivated to introduce the gelling capacity taught by Watts et al. into the solutions of Eriksen et al. because this would improve the duration of the desired plasma concentration of the active agent delivered from the compositions in the method taught by Eriksen et al. through enhanced retention of the agent in the nasal cavity. As Watts et al. teach, "It would be most beneficial, due to ease of use and of administration, to have available a simple solution spray system that was suitable for the administration of drugs to the nose and, better still, for the drugs administered via such a system to have a long retention in the nasal cavity," (p. 2, lines 23-26). The person of ordinary skill in the art would have expected success because the mucoadhesives are designed for effecting retention of active agents in nasal spray solutions in the nasal cavity upon administration.

31. Claims 16 and 53-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eriksen et al. (Applicant-cited reference on IDS: Eriksen, J. et al. *J. Pharm. Pharmacol.* **1989**, *41*, 803-805.) in view of Koochaki (Applicant-cited reference on IDS: EP 0 571 671 A1).

32. Eriksen et al. teach the composition comprising dextrose and buprenorphine hydrochloride, as discussed above. The concentration of buprenorphine in the composition is 2 mg/ml, which is within the instantly claimed ranges. Eriksen et al. teach preparation of the composition and incorporation of said composition into a spray device for intranasal delivery ("The spray-device and the buprenorphine-spray solution" on p. 803). Eriksen et al. also teach a method of inducing analgesia comprising administering said composition intranasally ("Procedure" section on pp. 803-4).

33. Eriksen et al. do not teach the solutions as further comprising chitosan or hydroxypropylmethyl cellulose (HPMC), or as having a pH from 3 to 4.8.

34. Koochaki teaches a composition comprising a drug and a pharmaceutical carrier, wherein the carrier comprises a non-ionic cellulose ether, preferably HPMC, and a chitin-derived polymer, which may be chitosan (p. 2, lines 38-44; Example 1; Example 2; claims 1-3 and 6). Koochaki teaches that the compositions are "for application to the mucosa of the nasal cavity." (claim 1). Koochaki teaches a method of incorporating the HPMC and chitosan into a composition containing a drug and adjusting the pH to about 4.5 (Example 1).

35. It would have been obvious to a person of ordinary skill in the art at the time of invention to modify the procedure for preparing the buprenophine nasal spray

composition of Eriksen et al. in order to incorporate chitosan and HPMC as taught by Koochaki, to modify the pH as taught by Koochaki, to incorporate the composition into a spray device, and to administer the composition in a method of inducing analgesia to arrive at the instantly-claimed invention.

36. The person of ordinary skill in the art would have been motivated to incorporate the mucoadhesives of Koochaki into the solution of Eriksen et al. because, as taught be Watts et al., this would improve retention of the drug in the nasal cavity after administration, thus improving the duration of the desired plasma concentration of the active agent (see above). The person of ordinary skill in the art would not even need to look to Watts et al. for motivation because it is very well known in the art that increasing the retention of an active compound in the nasal cavity that is administered intranasally will improve the time that the compound is available to be absorbed in the body. The person of ordinary skill in the art would have expected success absent evidence to the contrary because chitosan and HPMC are routinely used pharmaceutical excipients that would be expected to be compatible with buprenorphine.

37. Claims 19 and 60-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eriksen et al. (Applicant-cited reference on IDS: Eriksen, J. et al. *J. Pharm. Pharmacol.* **1989**, *41*, 803-805.) in view of Williams et al. (Applicant-cited reference on IDS: WO 02/00195 A2, January 3, 2002).

38. Eriksen et al. teach the composition comprising dextrose and 2 mg/ml buprenorphine as buprenorphine hydrochloride, as well a method of preparing said

composition, a nasal spray device for intranasal administration of said composition, and a method of inducing analgesia comprising intranasally administering said composition, as discussed above.

39. Eriksen et al. do not teach the compositions as further comprising chitosan and polyoxyethylene-polyoxypropylene copolymers, or the pH of the solution as being from 3 to 4.8.

40. Williams et al. teach, "A composition comprising a mucoadhesive, a local anesthetic or a pharmaceutically-acceptable salt thereof, and an opioid or a pharmaceutically-acceptable salt thereof." (claim 1; Examples 1 and 2). Williams et al. further teach, "the mucoadhesive is a block polymer of ethylene oxide and propylene oxide." (Claim 6 and p. 7, line 10 –p. 8, line 11). Williams et al. teach, "Preferably, the pH of the composition is within the range of from about 2 to about 9, more preferably, about 3 to about 7, even more preferably about 4 to about 5, and optimally about 4.5." (p. 10, lines 26-30).

41. It would have been obvious to a person of ordinary skill in the art at the time of invention to modify the procedure for preparing the buprenophine nasal spray composition of Eriksen et al. to incorporate the mucoadhesives of Williams et al. into the solution taught by Eriksen et al., to modify the pH as taught by Williams et al., to incorporate the composition into a spray device, and to administer the composition in a method of inducing analgesia, to arrive at the instantly-claimed invention.

The person of ordinary skill in the art would have been motivated to incorporate the mucoadhesives of Williams et al. into the solution of Eriksen et al. because, as taught

be Watts et al., this would improve retention of the drug in the nasal cavity after administration, thus improving the duration of the desired plasma concentration of the active agent by increasing retention of the agent in the nasal cavity (see above). As discussed above, the person of ordinary skill in the art would not need Watts et al. because the utility and purpose of nasal spray solutions for delivering pharmaceuticals is well-recognized in the art. The person of ordinary skill would have further been motivated with a reasonable expectation of success because Williams et al. teach that buprenorphine is a suitable opioid for incorporation into compositions containing the specified mucoadhesives for intranasal delivery (p. 4, lines 11-26).

Double Patenting

42. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

43. Claims 1-6, 8-10, 12, 13, 16, 19, and 59 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 16, 19, 38-43, 45-47, 49, 50, and 56 of copending Application No. 10/508,315. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

44. The claims of '315 correspond to the instant claims in the following manner:

45. Claim 16 of '315 is identical to the instant claim 16.

46. Claim 19 of '315 is identical to the instant claim 19.

47. Claims 38-43, 45-47, and 49 of '315 are identical, respectively, to the instant claims 1-6, 8-10, and 12.

48. Claim 50 of '315 is identical to the instant claim 13.

49. Claim 56 of '315 is identical to the instant claim 59.

50. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

51. Claims 7, 11, 38, 39, 41, 48-55, 57-62, and 64-66 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13-34, 38-50, and 56-59 of copending Application No. 10/508,315.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they are drawn to obvious variants of the same subject matter.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

52. Claim 48 of '315 teaches, "An aqueous solution suitable for intranasal administration, which comprises 0.1 to 10 mg/ml of buprenorphine or a physiologically acceptable salt or ester thereof and from 5 to 40 mg/ml of a pectin having a degree of esterification of less than 50%; which solution has a pH of from 3 to 4.2, is substantially free from divalent metal ions and gels on the nasal mucosa," said composition having an osmolality of from 0.25 to 0.4 osmol/kg.

53. '315 does not teach the solution as having an osmolality of from 0.35 to 0.5 osmol/kg.

54. It would have been obvious to a person of ordinary skill in the art at the time the invention was made to adjust the osmolality to within a range that is considered suitable within the art for intranasal delivery. Furthermore, the small change of the osmolality range does not constitute a patentably distinct composition because it does not alter the properties of the compositions with respect to their intended use.

55. Claims 53-54 of '315 teach a nasal delivery device, and more specifically a spray device, which is loaded with the composition of claim 16 of '315, namely, "An aqueous solution suitable for intranasal administration, which comprises: (a) from 0.1 to 10 mg/ml of buprenorphine or a physiologically acceptable salt or ester thereof, (b) from 0.1 to 20

mg/ml of a chitosan, and (c) from 0.1 to 15 mg/ml of hydroxoropylmethylcellulose; which solution has a pH of from 3 to 4.8."

56. '315 does not teach a nasal delivery device, or a nasal device which is a spray device, loaded with the composition of claim 38 of '315, which is the same composition as claim 1 of the instant application.

57. It would have been obvious to a person of ordinary skill in the art at the time invention was made to put the composition of claim 38 of '315 into the same nasal delivery device taught in claims 53-54 of '315 for administering the composition of claim 16 of '315 to make the invention of claims 38-39 of the instant application.

58. The person of ordinary skill in the art would have been motivated to put the composition of claim 16 of '315 into the nasal delivery device or spray device taught in claims 53-54 of '315 because it would allow them to deliver the same active agent, buprenorphine, in the same method of inducing analgesia, and would have expected success absent evidence to the contrary.

59. Claim 56 of '315 teaches a method of inducing analgesia which comprises intranasal administration of the composition of claim 16 of '315.

60. '315 does not teach a method of inducing analgesia comprising intranasal administration of the composition of claim 38 of '315, which is the same composition as claim 1 of the instant application.

61. It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the composition taught in claim 38 of '315 in the method of

inducing analgesia taught in claim 56 of '315 to make the invention of claim 41 of the instant application.

62. The person of ordinary skill in the art would have been motivated to use the composition taught in claim 38 of '315 in the method of claim 56 of '315 because they contain the same active agent, buprenorphine, and would have expected success absent evidence to the contrary.

63. Claims 1, 13, 16, 19, 38-39, 41, 56-59, and 64-66 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2, 8, and 12 of U.S. Patent No. 6,387,917. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants of the same invention.

64. '917 teaches a composition adapted for intranasal delivery comprising a methane sulphonate salt of an opioid analgesic, and further comprising chitosan or a salt or derivative thereof (claims 1 and 2). '917 also teaches a method of treating pain comprising administering to the nose a methane sulphonate of an opioid analgesic (claim 8), and a nasal drug delivery device containing as a drug a methane sulphonate salt of an opioid analgesic (claim 12).

65. '917 does not teach use of buprenorphine in the compositions or methods as the opioid analgesic.

66. It would have been obvious to a person of ordinary skill in the art at the time of invention to generate a methane sulphonate salt of buprenorphine, put it into the

composition suitable for intranasal delivery taught in '917, place the composition into the nasal delivery device taught in '917, and use the composition in the method of treating pain taught in '917, to make the inventions the current application.

67. The person of ordinary skill in the art would have been motivated to use buprenorphine in the compositions and methods of '917 because '917 teaches compositions for intranasal administration which comprise analgesics generally, and buprenorphine is a well known analgesic that is administered intranasally. The person of ordinary skill in the art would have been further motivated because '917 states, this would "provide an increased absorption of the drug." (column 2, lines 66-67). The person of ordinary skill would have expected success absent evidence to the contrary.

Response to Arguments

68. Applicant's arguments filed December 27, 2006, have been fully considered but they are not persuasive.

69. Regarding the rejection of claims 1-15, 38, 39, and 41 under 35 USC § 103 over Eriksen et al. (Applicant-cited reference on IDS: Eriksen, J., et al. *J. Pharm. Pharmacol.* **1989**, *41*, 803-805) in view of Watts et al. (WO 98/47535), Reich et al. (Reich, I., et al. "Tonicity, Osmoticity, Osmolality and Osmolarity" in Remington: The Science and Practice or Pharmacy, Nineteenth Edition, Volume 1. (1995) Easton, PA: Mack. pp. 613-615), and Nairn (Nairn, J. G. "Solutions, Emulsions, Suspensions and Extracts" in Remington: The Science and Practice or Pharmacy, Nineteenth Edition, Volume 2. (1995) Easton, PA: Mack. pp. 1495, 1496 and 1502), Applicant alleges that the

compositions of Eriksen et al. differ from the composition of the instant claims in that dextrose is present. It is noted that the instant claim 12, which depends from claim 1, specifies that the compositions of the instant application comprise dextrose. Also, the formulations disclosed in the instant specification comprise dextrose. Eriksen et al. clearly teach that their formulations comprise dextrose (p. 804). Thus, there is no discrepancy in this sense.

70. Applicant goes on to state that the compositions of Eriksen et al. differ from the instantly claimed formulations comprising buprenorphine and pectins because there are no pectins in the formulations, the pH is different, there is no teaching of the absence of divalent metal cations, and there is no teaching that the formulations gel on the nasal mucosa. Regarding the pH and pectins, Watts et al. teach the herein-claimed pectins and a pH substantially close to the herein-claimed range for sustained delivery of agents on the nasal mucosa. Regarding the fact that Eriksen et al. are silent with respect to their formulations being free of divalent metal cations, the Examiner respectfully points out that a key factor in determining obviousness under § 103 is "the level of ordinary skill in the pertinent art". If the standard of the § 103 rejection was what would have been obvious to a person of no skill in the art, it might have been assumed that tap water could be used in the formulations of Eriksen et al. However, it is a highly routine practice in the art to use deionized or distilled water in scientific experiments where the presence of metal ions or other contaminants might interfere with the results, particularly for something as sensitive as a pharmaceutical formulation. Further, Watts et al. teach that using the herein-claimed pectins causes the nasal spray solutions to gel

on the nasal mucosa in the absence of metal ions (Abstract). Why would the person of ordinary skill in the art assume that tap water should be used if Watts et al. teach that nasal spray formulations comprising their mucoadhesives gel in the absence of metal ions? This teaching also addresses Applicant's limitation that the instantly claimed formulations comprising the pectins of Watts et al. gel on the mucosa. Applicant goes on to discuss the relatively high maximum plasma concentrations that are rapidly achieved and well sustained. It is noted that these are not limitations in the claims. Further, even if these were limitations in the claims, they are inherent properties of the formulations suggested by Eriksen et al. in view of Watts et al.

71. Applicant finally argues that Watts et al. teach away from a formulation with the desired properties of a rapid onset of analgesia, a closer to optimum level of analgesia, or analgesia that is well sustained because Watts et al. teach that if the formulation is for local administration, the formulation should not enhance transmucosal absorption, and if for systemic administration, the formulation should not give rise to any significant plasma concentration. Firstly, it is noted that these are not limitations in the claims. Secondly, it is pointed out that on p. 3, ll. 16-25, Watts et al. teach that incorporation of the pectins into nasal spray solutions produces a simple nasal delivery system that can be used to modify (increase or decrease) the absorption characteristics when administering drugs systemically or locally. Watts et al. teach that when the drugs are to be administered locally, the system should not enhance absorption to effect increased systemic delivery. However, this is only one of the options for modulating the absorption characteristics, and it is particularly only relevant to local delivery of the

drugs. Because buprenorphine is for systemic delivery, it would have been obvious to a person of ordinary skill in the art that the pectin gelling agents could be used to increase systemic delivery of the active compounds, if desired. Also, at the Applicant-cited passage p. 14, l. 12 on, Watts et al. teach that the nasal spray composition can be formulated to alter (increase or decrease) the rate of transport in the general circulation, not only decrease as Applicant asserts.. See also p. 14, lines 20-24, where Watts et al. teach that the "invention may thus be used for the modification of the systemic absorption of mucosally administered drugs." Further, on p. 14, Watts et al. suggest that the formulation can be used to deliver apomorphine and fentanyl, which are systemic analgesics similar to buprenorphine. Thus, Watts et al. do not teach away from systemic administration of buprenorphine with their mucoadhesives.

72. Regarding the rejection of claims 16 and 53-59 under 35 USC § 103 over Eriksen et al. (Applicant-cited reference on IDS: Eriksen, J., et al. *J. Pharm. Pharmacol.* **1989**, *41*, 803-805) in view of Koochaki (Applicant-cited reference on IDS: EP 0 571 671 A1), Applicant argues that the composition of Eriksen et al. differs from the present formulations in that is comprises dextrose, does not contain chitosan and hydroxypropylmethylcellulose (HPMC), and has a different pH. It is noted that because of the open language "comprising" in the claims, the inclusion of dextrose in the instantly claimed formulations is not precluded. Further, the exemplified formulations in the specification comprise dextrose. Thus, the compositions of Eriksen et al. do not differ from the instantly claimed formulations in this sense.

73. Regarding the presence of chitosan and HPMC, the previous Office Action acknowledges that Eriksen et al. do not teach these additives in the formulations. This is why the Koochaki reference was applied. Koochaki teaches the addition of the mucoadhesives chitosan and HPMC to retain the active agent in the nasal cavity for sustained delivery. Although Koockaki does teach that the formulations are in a powder form, it would have been obvious to the person of ordinary skill in the art that the mucoadhesives chitosan and HPMC could also be used in a solution that gels upon introduction into the nasal cavity to achieve sustained delivery by simply lowering the concentration of the mucoadhesives. Koochaki in fact teaches that this is a known strategy in the pharmaceutical formulation art (p. 2, lines 16-22). Koochaki does not teach that this strategy in ineffective. He merely teaches that the powder formulation is an alternative to the solution formulation that gels on the mucosa. The optimal concentration of the mucoadhesives that would allow sprayability and mucoadhesion could be arrived at through routine experimentation by the ordinary skilled artisan. Thus, it would have been obvious that the mucoadhesives they teach, chitosan and HPMC, could be used in nasal spray solutions that gel on the mucosa to achieve sustained release of the active agent. Regarding the pH of the compositions, it was noted in the previous Office Action that Koochaki teaches a pH of 4.5, which is within the herein-claimed range.

74. Regarding the rejection of claims 19 and 60-66 under 35 USC § 103 over Eriksen et al. (Applicant-cited reference on IDS: Eriksen, J., et al. *J. Pharm. Pharmacol.* **1989**, *41*, 803-805) in view of Williams et al. (Applicant-cited reference on IDS: WO 02/00195),

Applicant argues that the ordinary skilled artisan would not be motivated to combine Eriksen et al. and Williams et al. to arrive at the instantly claimed invention because Williams et al. is directed to local delivery of analgesics, whereas the instantly claimed formulations are for systemic delivery of the analgesic. It is noted that the intended use of the composition does not lend patentability to the composition. Williams et al. exemplify buprenorphine as a suitable opioid for formulation with the polyoxyethylene-polyoxypropylene copolymer mucoadhesives (p. 4, lines 11-13). Regardless of whether the formulation is for systemic or local administration of the buprenophine, the compositions are identical. Eriksen et al. teach that introduction of buprenorphine into the nasal cavity achieves systemic delivery of the active agent for inducing analgesia. Thus, the person of ordinary skill in the art would understand that using the excipients of Williams et al. in a nasal spray solution containing buprenorphine would achieve sustained systemic delivery of the agent through the nasal mucosa, as opposed to sustained local delivery through the buccal mucosa. Finally, Williams et al. teach that chitosan can also be incorporated with the polyoxyethylene-polyoxypropylene copolymer mucoadhesives (p. 7, ll. 10-11).

75. Regarding the rejection of claims 1, 13, 16, 19, 38-39, 41, 56-59, and 64-66 on the ground of nonstatutory obviousness-type double patenting over claims 1-2, 8, and 12 of U.S. Patent No. 6,387,917, Applicant argues that there is no teaching of "formulations for the nasal cavity that comprise buprenorphine or a salt thereof". As pointed out in the previous Office Action, '917 teaches a composition adapted for nasal delivery comprising a methane sulphonate salt of an opioid analgesic (claims 1). At col.

3, ll. 21-25, buprenorphine is exemplified as an opioid analgesic for incorporation into the nasal delivery formulation. Thus, '917 teaches "formulations for the nasal cavity that comprise buprenorphine or a salt thereof", and the double-patenting rejection is properly maintained.

Conclusion

76. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin Capps whose telephone number is (571) 272-8646. The examiner can normally be reached on Monday-Friday, 7:30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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KC

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